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10/526,073	02/28/2005	Shigekazu Hokazono	HOKAZONO1	8315

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,073	HOKAZONO ET AL.	
	Examiner	Art Unit	
	DELIA M. RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 6-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1* is/are allowed.

6)☒ Claim(s) *7-9* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *alignment,GenBank entry*.

DETAILED ACTION

Status of the Application

Claims 1, 6-9 are pending.

Applicant's amendment of claim 1, addition of claims 7-9, and amendments to the specification as submitted in a communication filed on 10/7/2008 is acknowledged.

Claims 1, 6-9 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

1. Claim 6 is objected to due to the recitation of "an isolated polypeptide having a thermostable ribonuclease H activity obtained by culturing a transformant into which a plasmid pApr108 harbored by *Escherichia coli* HMS174/pApr108…is transferred" for the following reasons. While the Examiner has interpreted this term to imply that the isolated polypeptide having thermostable ribonuclease H activity is the thermostable ribonuclease H encoded by the plasmid pApr108, it is suggested that to clearly indicate that the polypeptide having a thermostable ribonuclease H activity is that encoded by plasmid pApr108 and not any thermostable ribonuclease H which can be produced by the transformant independently from what is encoded in plasmid pApr108, the term be amended to recite, for example, of "an isolated polypeptide having a thermostable ribonuclease H activity encoded by plasmid pApr108, wherein said polypeptide is obtained by culturing a transformant into which plasmid pApr108 harbored by *Escherichia coli* HMS174/pApr108…is transferred". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection necessitated by the addition of claims 7 and 9.

4. Claim 7 is indefinite in the recitation of "90% homology with the nucleic acid sequence of SEQ ID NO: 2" for the following reasons. The term is unclear and confusing in the absence of a definition providing the intended meaning of the term or the intended parameters required to determine the required homology value. While one could argue that the term "sequence homology" can be interpreted as "sequence identity", as known in the art, these terms are not equivalent. The calculation of sequence homology takes into consideration the type of mismatches, i.e. even mismatches contribute to the % homology value, whereas mismatches do not have any weight in the calculation of sequence identity, i.e. only exact matches contribute to the % identity value. Thus, if there is no indication that the term "homology" is intended to mean "identity", and the specification does not provide the specific parameters intended in the calculation of sequence homology (e.g., PAM matrices), one of skill in the art cannot determine the scope of the term "90% homology" because one could have a nucleic acid sequence which is 90% sequence homologous to a reference sequence based on a particular matrix/set of parameters, and at the same time, not 90% sequence homologous to the same reference sequence if other matrices/parameters are used. For examination purposes, it will be assumed that the term reads "90% sequence identity with the nucleic acid of SEQ ID NO: 2". Correction is required.

5. Claim 9 is indefinite in the recitation of "nucleic acid which is amplified by PCR reaction using primers having nucleic acid sequences…..from DNA of the genus *Archaeoglobus*" because it is unclear if the term "DNA of the genus *Archaeoglobus*" refers to the source of the primers or the source of the nucleic acid template to be amplified. For examination purposes, it will be assumed that the term reads "nucleic acid endogenously found in organisms from the genus Archaeoglobus which is amplified by PCR reaction using primers having nucleic acid sequences…..for one minute." Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 8-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection necessitated by Applicant's addition of claims 8 and 9.

Claim 8 is directed to a genus of polypeptides having thermostable ribonuclease H activity (1) encoded by a nucleic acid which hybridizes under the specific recited conditions to a nucleic acid comprising any fragment of the polynucleotide of SEQ ID NO: 2 or full complements thereof, and (2) having conserved portions encoded by a nucleic acid amplified by PCR reaction using the primers of SEQ ID NO: 3 and 4 under specific conditions. It should be noted that the term "nucleic acid having a nucleotide sequence of SEQ ID NO: 2", in its broadest reasonable interpretation, encompasses nucleic acids comprising any fragment of SEQ ID NO: 2 because the term "a nucleotide sequence of SEQ ID NO: 2" can be read as "any sequence within SEQ ID NO: 2". Claim 9 is directed to a genus of polypeptides having thermostable ribonuclease H activity wherein said polypeptides are encoded by nucleic acids endogenously found in organisms of the genus *Archaeoglobus* which are amplified by PCR reaction using the primers and conditions recited. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

While the Examiner has been able to find support for a nucleic acid which hybridizes under the conditions recited to the nucleic acid of SEQ ID NO: 2 and encodes a protein having thermostable ribonuclease H activity, and nucleic acid amplification of genomic DNA from *Archaeoglobus profundus* using the primers and conditions recited, the Examiner has been unable to find support for (A) a subgenus of proteins having thermostable ribonuclease H activity wherein said proteins are (1) encoded

by nucleic acids which hybridize under the conditions recited to the nucleic acid of SEQ ID NO: 2 or nucleic acids comprising any fragment of SEQ ID NO: 2, **and** (2) have conserved portions encoded by a nucleic acid which is amplified using the primers and conditions recited, or (B) a subgenus of proteins having thermostable ribonuclease H activity wherein said proteins are encoded by nucleic acids endogenously found in organisms of the genus *Archaeoglobus* which are amplified by PCR reaction using the primers and conditions recited. Thus there is no indication that the recited subgenera of proteins were within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

8. Claims 7-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is necessitated by Applicant's addition of claims 7 and 8.

9. Claims 7 and 8 are directed to a genus of proteins encoded by nucleic acids which are structural variants of the polynucleotide of SEQ ID NO: 2, wherein said variants hybridize under the conditions recited to a polynucleotide comprising any fragment of SEQ ID NO: 2 or to the polynucleotide of SEQ ID NO: 2, or wherein said variants have at least 90% sequence identity to the polynucleotide of SEQ ID NO: 2. See Claim Rejections under 35 USC 112, first and second paragraphs, for claim interpretation and discussion of scope. It should be noted that in claim 8, the limitation recited in part (b) does not further limit the genus of proteins recited in view of the fact that part (b) does not define the template to be amplified, thus the nucleic acid amplified by PCR reaction can be any nucleic acid.

10. In the instant case, while the claims are defined structurally and functionally, neither the specification nor the art provide a structure/function correlation which would allow one of skill in the art to envision the structure of those variants which meet the recited functional characteristics. As known in

the art, structural homology is not necessarily a surrogate for conservation of function. The art, as previously discussed, teaches several examples of how even small changes in structure can lead to changes in enzymatic function. See the teachings of Witkowski et al., Seffernick et al. and Branden et al. first discussed in the Non Final action mailed on 9/5/2007. While the argument can be made that ribonuclease H is known in the art, it is noted that the claims require a thermostable ribonuclease H. Neither the art nor the specification provide the structural features required in any protein having ribonuclease H activity such that it would be thermostable. Without an art-recognized structure/function correlation, one of skill in the art can not identify those variants expected to encode proteins having the recited function. As such, one cannot reasonably conclude that the disclosure of the polypeptide of SEQ ID NO: 1 or the disclosure of the polynucleotide of SEQ ID NO: 2 are representative of the entire genus of proteins encompassed by the claims. Applicant is directed to Example 11A of the newly revised Written Description guidelines for further guidance.

11. Claims 7-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 1, does not reasonably provide enablement for proteins having thermostable ribonuclease H activity encoded by nucleic acids which are structural variants of the polynucleotide of SEQ ID NO: 2, wherein said variants hybridize under the conditions recited to a polynucleotide comprising any fragment of SEQ ID NO: 2 or to the polynucleotide of SEQ ID NO: 2, or wherein said variants have at least 90% sequence identity to the polynucleotide of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is necessitated by Applicant's addition of claims 7 and 8.

12. Applicant argues that the scope of claims 7 and 8 is fully enabled by the teachings of the specification and the prior art and cite specific sections of several issued patents in support of the

argument that it would not require undue experimentation to enable the entire scope of Applicant's invention.

13. Applicant's arguments have been fully considered but are not deemed persuasive to avoid the rejection of claims 7-8. The examiner acknowledges the cited patents. It is noted, however, that each application is examined on its own merits and a review of the records of other patent applications or a discussion of the examination details of other patent applications would be improper herein. New claims 7-8 are directed to proteins having thermostable ribonuclease H activity encoded by nucleic acids which are structural variants of the polynucleotide of SEQ ID NO: 2, wherein said variants hybridize under the conditions recited to a polynucleotide comprising any fragment of SEQ ID NO: 2 or to the polynucleotide of SEQ ID NO: 2, or wherein said variants have at least 90% sequence identity to the polynucleotide of SEQ ID NO: 2. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation and the previous written description rejection above for discussion of scope. As indicated above, while the claims are limited structurally and functionally, neither the specification nor the art provide a structure/function correlation which would allow one of skill in the art to determine which of the essentially infinite number of structural variants of the polynucleotide of SEQ ID NO: 2 encompassed by the claims encode a protein having the desired thermostable ribonuclease H activity. In the absence of such correlation or some knowledge or guidance as to how to select those variants most likely to encode the desired proteins, one of skill in the art would be left to test virtually an infinite number of species and determine which ones encode the recited proteins. Using the equation of Meinkoth and Wahl previously provided, $Tm = 81.5\ ^{o}C + 16.6 \times \log_{10}[Na+] + 0.41 \times (\%GC) - .61 \times (\%form) - 500/L$, the corresponding Tm for the polynucleotide recited is approximately 73.2 °C assuming a G+C content of 50% and neglecting the term 500/L (0.1xSSC and 50 C). A wash at 50 °C and 0.1xSSC is equivalent to approximately 23.2% mismatching (23.2% = 73.2 °C – 50°C). This level of mismatching amounts to 148 nucleotides which can be modified (148 = 0.232x636) within SEQ ID NO: 2 (636 bp). Thus, the genus of polynucleotides recited can potentially encompass polynucleotides encoding proteins which are 29.9%

sequence identical to the polypeptide of SEQ ID NO: 1 since the 148 mismatches can potentially alter 148 codons (29.9% = 100% -148x100/211; SEQ ID NO: 1 has 211 amino acids). Even if it is assumed that only a third of the 148 mismatches (50) would affect codons, the genus of polynucleotides recited encompass polynucleotides encoding proteins having 76.3% sequence identity to the polypeptide of SEQ ID NO: 1. If one were to calculate the total number of species having, for example, 90% sequence identity to the polynucleotide of SEQ ID NO: 2, as is the case in claim 7 as interpreted, using the previously provided formula $N!x19^{A}/(N-A)!/A!$, the total number of variants amount to $636!x19^{64}/(636-64)!/64!$ $5.44x10^{170}$ variants. Clearly, this number would increase if the % sequence identity is lowered. It is reiterated herein that while enablement is not precluded by the necessity for routine experimentation, if an extremely large amount of screening is required, as is the case herein, the specification and/or the art should provide guidance as to how to recognize those variants most likely to encode the desired protein to reduce the amount of experimentation. Since this guidance/knowledge has not been provided, one cannot reasonably conclude that the claimed invention is fully enabled by the teachings of the specification.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Klenk et al. (PIR accession number E69327, 1997). The teachings of this reference have been provided in a previous Office action. The ribonuclease H and polynucleotide of Klenk et al. are from *Archeoglobus fulgidus*. Claim 9 is directed to a protein having thermostable ribonuclease H activity encoded by a nucleic acid endogenously found in an organism of the genus *Archeoglobus*, wherein said nucleic acid is amplified by PCR using specific primers under specific conditions. See Claim Rejections under 35 USC 112, second paragraph,

for claim interpretation. Since the limitation regarding amplification via PCR is a product by process limitation, the patentability of the claimed protein is determined solely on the characteristics of the product. In the absence of evidence to the contrary, and in view of the fact that the polynucleotide of Klenk et al. is 61% sequence identical to the polypeptide of SEQ ID NO: 2 (61%= 389x100/636; see attached alignment), it would be reasonable to expect the polynucleotide of Klenk et al. to be amplified via PCR under the conditions recited if genomic DNA from *Archeoglobus fulgidus* is used as template. As such, the polypeptide of Klenk et al, which is a thermostable ribonuclease H encoded by the polynucleotide of Klenk et al. would anticipate the instant claim as written.

Allowable Subject Matter

16. Claim 1 appear to be allowable over the prior art of record.

17. Claim 6 is objected to but would be allowable over the prior art of record if amended as suggested.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez
Primary Patent Examiner
Art Unit 1652

DR
December 18, 2008